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ATTORNEY'S DOCKET NUMBER: 4-21233/A

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/367361

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP98/00794	12 February 1998 (12.02.98)	14 February 1997 (14.02.97)

TITLE OF INVENTION
OXACARBAZEPINE FILM-COATED TABLETS

APPLICANT(S) FOR DO/EO/US
BURKHARD SCHLÜTERMANN

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau. (See Form PCT/IB/308)
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C.371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An executed Declaration and Power of Attorney (original or copy) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included.

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☐ Other items or information:

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/367361	PCT/EP98/00794	4-21233/A

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(a) (1)-(5)):

		CALCULATIONS PTO USE ONLY
Search Report has been prepared by the EPO or JPO	$840	
International preliminary examination fee paid to USPTO (37 CFR 1.482)	$670	
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))	$760	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$970	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$96	

ENTER APPROPRIATE BASIC FEE AMOUNT = $ 840

Surcharge of **$130** for furnishing the oath of declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)). $

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE	
Total claims	10	- 20 =	0	X $ 18	$
Independent claims	6	- 3 =	3	X $ 78	$ 234
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ $ 260	$

TOTAL OF ABOVE CALCULATIONS = $ 1,074

Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28). $

SUBTOTAL = $ 1,074

Processing fee of **$130** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). + $

TOTAL NATIONAL FEE = $ 1,074

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40** per property + $

TOTAL FEES ENCLOSED = $ 1,074

Amount to be: refunded $

charged $

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge Deposit Account No. 19-0134 in the name of Novartis Corporation in the amount of $1,074 to cover the above fees. A duplicate copy of this form is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0134 in the name of Novartis Corporation.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to the address associated with Customer No. 001095, which is currently:

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
BURKHARD SCHLÜTERMANN
INTERNATIONAL APPLICATION NO: PCT/EP98/00794
FILED: 12 FEBRUARY 1998
U.S. APPLICATION NO: Not Yet Known
35 USC §371 DATE: Herewith
FOR: OXACARBAZEPINE FILM-COATED TABLETS

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to calculation of the national filing fees, please amend the application as follows:

IN THE CLAIMS

Please amend the following claims:

Claim 5, line 1, delete "either claim 3 or claim 4" and substitute therefor --claim 3--.

REMARKS

Claim 5 has been amended to eliminate multiple dependencies.

Early and favorable consideration of the claims is respectfully awaited.

Respectfully submitted,

William K. Wissing
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Reg. No. 34,757

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Date: August 11, 1999

Oxacarbazepine Film-Coated Tablets

The present invention relates to formulations of oxcarbazepine, in particular film-coated tablets and to processes for the production of said formulations.

Oxcarbazepine, 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide, like ®Tegretol [(Novartis) carbamazepine: 5H-dibenz[b,f]azepine-5-carboxamide)], is an agent of first choice in the treatment of convulsions. The known dosage forms, such as tablets and liquid dosage forms, e.g.suspensions, are suitable for ensuring a uniform concentration of active ingredient in the blood, especially in the case of regularly recurring administration over a prolonged period of treatment. Nevertheless, it is always desirable to develop and improve upon existing formulations with respect to, for example bioavailability and compliance.

EP 0 646 374 discloses a formulation of oxacarbazepine which is coated with two layers (an inner and outer layer) containing pigments. The outer layer contains Iron Oxide. The double-coated tablet prevents inhomogeneous colouration of the formulation upon storage.

Despite the known forms of oxacarbazepine, it is always desirable to provide improved formulations.

We have now found formulations of oxacarbazepine which are easily processed into dosage forms and which may enhance the bioavailability of oxacarbazepine and increase compliance.

Accordingly, the invention provides in one of its aspects a formulation of oxacarbazepine comprising oxacarbazepine, preferably in a finely ground form, having a median particle size of approximately 2 to 12μm, perferably 4 to 12 μm, more preferably 4 to 10 μm and with a maximum residue on a 40 μm sieve of up to 5%, e.g. 2%.

The formulation according to the invention may contain pharmaceutically acceptable excipients commonly used in pharmaceutical formulations, e.g. for oral administration.

In a preferred embodiment according to the invention the formulation may be in the form of a film-coated tablet

which comprises,

a) a tablet core comprising a therapeutically effective dose of the oxacarbazepine, preferably in a finely ground form, having a median particle size of approximately from 2 to 12µm, preferably 4 to 12 µm, more preferably 4 to 10 µm with a maximum residue on a 40 µm sieve of up to 5%, e.g. 2 %, and further excipients that are suitable for the production of granules; and

b) a hydrophilic permeable outer coating.

The formulations, e.g. film-coated tablets according to the present invention use oxacarbazepine of fine particle size and narrow particle size distribution and as such may be formulated into dosage forms, e.g solid oral dosage forms such as tablets with relative ease. Furthermore, the fine particle size and narrow particle size distribution may also be beneficial in improving the bioavailablity of oxacarbazepine. Still further the formulations meet all customary requirements, such as storage stability and colour stability.

The colour stability may be achieved using only a single coating containing pigments rather than requiring a double coating containing pigments. This has the advantage of rendering the process of formulating the dosage forms relatively simple and efficient. Furthermore, for a given dosage size, e.g. 300mg lower amounts of pigment, e.g. Iron oxide (when employed) are required in the coating.

The invention provides in another of its aspects a process for the production of a film-coated tablet containing oxacarbazepine comprising the steps of forming the oxacarbazepine, having a median particle size of approximately from, 2 to 12 µm, preferably 4 to 12 µm, more preferably 4 to 10 µm with a maximum residue on a 40 µm sieve of up to 5%, e.g. 2 %, and optionally other excipients into a central core and coating said core with a hydrophilic permeable outer coating.

In a preferred aspect of the invention there is provided a process for the production of a film-coated tablet containing oxacarbazepine which comprises finely grinding

oxacarbazepine to a median particle size of approximately from 2 to 12 µm, preferably 4 to 12 µm, more preferably 4 to 10 µm with a maximum residue on a 40 µm sieve of up to 5%, e.g. 2 % and, with the admixture of excipients that are suitable for granulation processes, forming the oxacarbazepine into granules, compressing the granules to form tablet cores using conventional tabletting processes, and providing the cores with a hydrophilic permeable outer coating.

Within the scope of the description of the invention, the terms used hereinbefore and hereinafter are defined as follows:

The term "film-coated tablet" denotes a perorally administrable, single-dose, solid dosage form that can be produced by compressing oxacarbazepine with conventional tabletting excipients to form a tablet core using conventional tabletting processes and subsequently coating the core. The tablet cores can be produced using conventional granulation methods, for example wet or dry granulation, with optional comminution of the granules and with subsequent compression and coating. Granulation methods are described, for example, in *Voigt, loc. cit.*, pages 156-169.

Suitable excipients for the production of granules are, for example pulverulent fillers optionally having flow-conditioning properties, for example talcum, silicon dioxide, for example synthetic amorphous anhydrous silicic acid of the Syloid® type (Grace), for example SYLOID 244 FP, microcrystalline cellulose, for example of the Avicel® type (FMC Corp.), for example of the types AVICEL PH101, 102, 105, RC581 or RC 591, Emcocel® type (Mendell Corp.) or Elcema® type (Degussa); carbohydrates, such as sugars, sugar alcohols, starches or starch derivatives, for example lactose, dextrose, saccharose, glucose, sorbitol, mannitol, xylitol, potato starch, maize starch, rice starch, wheat starch or amylopectin, tricalcium phosphate, calcium hydrogen phosphate or magnesium trisilicate; binders, such as gelatin, tragacanth, agar, alginic acid, cellulose ethers, for example methylcellulose, carboxymethylcellulose or hydroxypropylmethylcellulose, polyethylene glycols or ethylene oxide homopolymers, especially having a degree of polymerisation of approximately from 2.0×10^3 to 1.0×10^5 and an approximate molecular weight of about from 1.0×10^5 to 5.0×10^6, for example excipients known by the name Polyox® (Union Carbide), polyvinylpyrrolidone or povidones, especially having a mean molecular weight of

approximately 1000 and a degree of polymerisation of approximately from 500 to 2500, and also agar or gelatin; surface-active substances, for example anionic surfactants of the alkyl sulfate type, for example sodium, potassium or magnesium n-dodecyl sulfate, n-tetradecyl sulfate, n-hexadecyl sulfate or n-octadecyl sulfate, of the alkyl ether sulfate type, for example sodium, potassium or magnesium n-dodecyloxyethyl sulfate, n-tetradecyloxyethyl sulfate, n-hexadecyloxyethyl sulfate or n-octadecyloxyethyl sulfate, or of the alkanesulfonate type, for example sodium, potassium or magnesium n-dodecanesulfonate, n-tetradecanesulfonate, n-hexadecanesulfonate or n-octadecanesulfonate, or non-ionic surfactants of the fatty acid polyhydroxy alcohol ester type, such as sorbitan monolaurate, monooleate, monostearate or monopalmitate, sorbitan tristearate or trioleate, polyoxyethylene adducts of fatty acid polyhydroxy alcohol esters, such as polyoxyethylene sorbitan monolaurate, monooleate, monostearate, monopalmitate, tristearate or trioleate, polyethylene glycol fatty acid esters, such as polyoxyethyl stearate, polyethylene glycol 400 stearate, polyethylene glycol 2000 stearate, especially ethylene oxide/propylene oxide block polymers of the Pluronics® (BWC) or Synperonic® (ICI) type.

Granules may be produced in a manner known *per se*, for example using wet granulation methods known for the production of "built-up" granules or "broken-down" granules.

Methods for the formation of built-up granules may operate continuously and comprise, for example simultaneously spraying the granulation mass with granulation solution and drying, for example in a drum granulator, in pan granulators, on disc granulators, in a fluidised bed, by spray-drying or spray-solidifying, or operate discontinuously, for example in a fluidised bed, in a batch mixer or in a spray-drying drum.

Preferred are methods for the production of broken-down granules, which may be carried out discontinuously and in which the granulation mass first forms a wet aggregate with the granulation solution, which aggregate is then comminuted or formed into granules of the desired particle size and the granules then being dried. Suitable equipment for the granulation step are planetary mixers, low and high shear mixers, wet granulation equipment including extruders and spheronisers include, for example, apparatus from the companies Loedige, Glatt, Diosna, Fielder, Collette, Aeschbach, Alexanderwerk, Ytron, Wyss & Probst, Werner & Pfleiderer, HKD, Loser, Fuji, Nica, Caleva and Gabler.

The granulation mass consists of comminuted, preferably ground, oxacarbazepine and the excipients mentioned above, for example pulverulent fillers, such as microcrystalline cellulose of the AVICEL type. AVICEL PH 102 is especially suitable. Depending on the method used, the granulation mass may be in the form of a premix or may be obtained by mixing the oxacarbazepine into one or more excipients or mixing the excipients into the oxacarbazepine. The wet granules are preferably dried, for example in the described manner by tray drying or in a fluidised bed.

According to an alternative process variant, tablet cores are produced using the so-called compacting or dry granulation method in which the active ingredient is compressed with the excipients to form relatively large mouldings, for example slugs or ribbons, which are comminuted by grinding, and the ground material is compressed to form tablet cores.

Suitable excipients for the compacting method are preferably those which are suitable for the conventional direct compression methods, for example dry binders, such as starches, for example potato, wheat and maize starch, microcrystalline cellulose, for example commercial products available under the trademarks Avicel®, Filtrak®, Heweten® or Pharmacel®, highly dispersed silicon dioxide, for example Aerosil®, mannitol, lactose, and also polyethylene glycol, especially having a molecular weight of from 4000 to 6000, crosslinked polyvinylpyrrolidone (Polyplasdone® XL or Kollidon® CL), crosslinked carboxymethylcellulose (Acdisol® CMC-XL), carboxymethylcellulose [Nymcel®, for example ZSB-10, (Nyma)], hydroxypropylmethylcellulose, for example the quality HPMC 603, carboxymethyl starch [Explotab® (Mendell) or Primojel® (Scholtens)], microcrystalline cellulose, for example Avicel® PH 102, dicalcium phosphate, for example Emcompress® or talcum. The addition of small amounts of, for example, lubricants, such as magnesium stearate, is also advantageous.

Compression to form tablet cores may be carried out in conventional tabletting machines, for example EK-0 Korsch eccentric tabletting machines or rotary tabletting machines. The tablet cores may be of various shapes, for example round, oval, oblong, cylindrical etc., and various sizes, depending on the amount of oxacarbazepine.

Oxacarbazepine is known. Its manufacture and therapeutic use as an anticonvulsive are described in German Auslegeschrift 2 011 087 which is incorporated herein by reference. A commercially advantageous process for the preparation of that active ingredient is described in European Patent Application No. 0 028 028 which is incorporated herein by reference. Commercially available dosage forms are provided for peroral administration, for example tablets comprising 300 and 600 mg of active ingredient. Those dosage forms are known by the trademark ®Trileptal (Novartis) and have been introduced in a large number of countries, such as Denmark, Finland, Austria and Belgium.

The median particle size of the oxacarbazepine is approximately from 2 to 12 µm, preferably 4 to 12 µm, more preferably 4 to 10 µm with a maximum residue on a 40 µm sieve of up to 5%, e.g. 2 %. In a preferred form of process, the median particle size of the oxacarbazepine is approximately from 4 to 12 µm, typically 6 to 8 µm with a maximum residue on a 40 µm sieve of up to 5%, e.g. 2 %.

The known particle size analysis methods are suitable for determining the median particle size, for example particle size measurement using light, for example light-scattering methods or turbidimetric methods, sedimentation methods, for example pipette analysis using an Andreassen pipette, sedimentation scales, photosedimentometers or sedimentation in a centrifugal force field, pulse methods, for example using a Coulter counter, or sorting by means of gravitational or centrifugal force. Those methods are described, *inter alia*, in *Voigt, loc. cit.*, pages 64-79.

In order to produce oxacarbazepine particles, e.g. crystals having the desired particle size, conventional comminution and de-agglomeration techniques may be used, for example grinding in an air-jet mill or impact mill, a ball mill, vibration mill, mortar mill or pin mill.

The hydrophilic permeable outer coating b) comprises a film-forming material that is permeable to water and intestinal juice and that may be swellable, and is soluble or at least to some extent soluble, in those fluids.

Water-permeable film-forming materials are, for example, hydrophilic mixtures of polyvinylpyrrolidone or of a copolymer of polyvinylpyrrolidone and polyvinyl acetate with

hydroxypropylmethylcellulose, mixtures of shellac with hydroxypropylmethylcellulose, polyvinyl acetate or copolymers thereof with polyvinylpyrrolidone, or mixtures of water-soluble cellulose derivatives, such as hydroxypropylmethylcellulose, and water-insoluble ethylcellulose.

The coating compositions may, if desired, be used in admixture with other additional excipients, such as talcum or silicon dioxide, for example synthetic amorphous silicic acid of the Syloid® type (Grace), for example SYLOID 244 FP, or wetting agents, for example sorbates or plasticisers, for example the afore-mentioned polyethylene glycols.

Elastic, film-like materials are especially hydrophilic, partially etherified cellulose derivatives.

Hydrophilic, partially etherified cellulose derivatives are, for example, lower alkyl ethers of cellulose having an average degree of molar substitution (MS) that is higher than one and lower than three and an average degree of polymerisation of approximately from 100 to 5000.

The degree of substitution is a measure of the substitution of the hydroxy groups by lower alkoxy groups per glucose unit. The average degree of molar substitution (MS) is an averaged value and indicates the number of lower alkoxy groups per glucose unit in the polymer.

The average degree of polymerisation (DP) is also an averaged value and indicates the average number of glucose units in the cellulose polymer.

Lower alkyl ethers of cellulose are, for example, cellulose derivatives that are substituted at the hydroxymethyl group (primary hydroxy group) of the glucose unit forming the cellulose chains and, where appropriate, at the second and third secondary hydroxy group by C_1-C_4alkyl groups, especially methyl or ethyl, or by substituted C_1-C_4alkyl groups, for example 2-hydroxyethyl, 3-hydroxy-n-propyl, carboxymethyl or 2-carboxyethyl.

Suitable lower alkyl ethers of cellulose are preferably cellulose derivatives that are substituted at the hydroxymethyl group (primary hydroxy group) of the glucose unit by the

mentioned C_1-C_4alkyl groups or by substituted C_1-C_4alkyl groups and at the second and, where appropriate, third secondary hydroxy group by methyl or ethyl groups.
Suitable lower alkyl ethers of cellulose are especially methylcellulose, ethylcellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, ethylhydroxyethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose (in salt form, for example in sodium salt form) or methylcarboxymethylcellulose (also in salt form, for example sodium salt form).

Preferred lower alkyl ethers of cellulose are ethylcellulose (DP: approximately from 150 to 1000, MS: approximately from 1.2 to 1.8), for example of the Aquacoat® type (FMC Corp.), hydroxyethylcellulose (DP: approximately from 120 to 1200, MS: approximately from 1.2 to 2.5) and hydroxypropylcellulose (DP: approximately from 200 to 3000, MS: approximately from 1.0 to 3.0).

Water-permeable film-forming materials also include cellulose acetate trimellitate (CAT), and methacrylic acid/methacrylate 1:1 or 1:2 copolymer, for example EUDRAGIT L and S, for example EUDRAGIT L 12.5 or S 12.5.

The film-forming material may be sprayed on in the form of an aqueous dispersion of redispersible cellulose acetate phthalate - CAP - (Aquateric®: FMC), of polyvinyl acetate phthalate - PVAP - (Coateric®: Colorcon), of hydroxypropylmethylcellulose phthalate - HPMCP - (Aquacoat® HP 50 or HP 55: Shin-Etsu) or also, especially, of acrylic acid/methacrylic acid copolymer partially esterified by C_1-C_4alkyl groups.

Also suitable is an acrylic acid/methacrylic acid 1:1 copolymer partially esterified by methyl and/or ethyl groups of the type EUDRAGIT L 30 D or water-dispersed EUDRAGIT L 100-55.

The film-forming materials may comprise additional excipients, such as, for example, plasticisers, for example triethyl citrate, for example Citroflex® (Pfizer), triacetin, various phthalates, for example diethyl or dibutyl phthalate, mixed mono- or di-glycerides of the Myvacet® type (Eastman), for example MYVACET 9-40, the polyethylene glycols mentioned hereinbefore, for example having a molecular weight of approximately from 6000 to 8000, and also ethylene oxide/propylene oxide block copolymers of the Pluronic® (BASF) or

Synperonic® (ICI) type, pulverulent mould release agents, for example magnesium trisilicate, starch or synthetic amorphous silicic acid of the SYLOID type, for example SYLOID 244 FP.

The hydrophilic permeable outer coating b) comprises white pigments, for example titanium dioxide pigments, preferably combined with iron oxide pigments. The iron oxide may be ferric or ferrous iron oxide, preferably Fe_2O_3 optionally in hydrated form. When iron oxide is employed, the amounts employed in the coating will depend upon the size of the particular dosage form. Preferably, the amount of iron oxide employed may be chosen from about 0.1mg per dosage form, e.g. tablet, to 1.6mg per dosage form, e.g. tablet, more preferably 0.3mg per dosage form, e.g. tablet to 0.9mg per dosage form, e.g. tablet.

The tablet cores may be coated with the hydrophilic permeable coating composition in a manner known *per se*, using conventional coating methods.

For example, the coating composition is dissolved or suspended in water in the desired quantity ratio. If desired, excipients, such as polyethylene glycol, are added. The solution or dispersion is sprayed onto the tablet cores together with other excipients, for example talcum or silicon dioxide, for example SYLOID 244 FP, for example using known methods, such as spray-coating in a fluidised bed, for example using the Aeromatic, Glatt, Wurster or Hüttlin (ball coater) system, or also in a coating pan in accordance with the methods known by the names Accela Cota or immersion coating.

Preferably, an aqueous dispersion comprising hydroxypropylmethylcellulose (cellulose HPMC) and pigments is sprayed on.

The formulations, e.g. film-coated tablets according to the invention are useful for their anticonvulsive action and are useful as monotherapy or as adjunctive therapy in the control, prevention or treatment of seizure, e.g. resulting from the onset of epilepsy, status epilepticus, cerebrovascular disorders, head injury and alcohol withdrawal.

The exact dose of oxacarbazepine and the particular formulation to be administered depend upon a number of factors, e.g. the condition to be treated, the desired duration of treatment and the rate of release of the oxacarbazepine. For example, the amount of oxacarbazepine required and the release rate thereof may be determined by in vitro or in

vivo techniques, determining how long a particular active agent concentration in the blood plasma remains at an acceptable level for a therapeutic effect.

Preferred regimes include for monotherapy, 150 to 600mg, e.g 300mg twice per day. Doses of from 1200 to 2400mg/day may be tolerated. Preferred regimes for adjunctive therapy include a starting dose of 300 mg/day. Doses from 600 to 2400 mg/day may be tolerated.

The following Examples illustrate the invention.

Example 1

Formulations

Example 1	(mg)	(mg)	(mg)
Tablet Core:			
Oxcarbazepine	150	300	600
Avicel PH 102	32,8	65,6	131,2
Cellulose HPM 603	4,2	8,4	16,8
Polyvinylpyrrolidone	10	20	40
Aerosil 200	0,8	1,6	3,2
Magnesium stearate	2,2	4,4	8,8
	200	**400**	**800**
Coating:			
Polyethylene glycol (PEG) 8000	0,832	1,331	2,162
Cellulose HPM 603	4,595	7,352	11,947
Talcum	3,327	5,323	8,649
Titanium Dioxide	0,935	1,496	2,431
Iron oxide, yellow	0,312	0,499	0,81

	10	16	26
Total	**210**	**416**	**826**

Mix the TRILEPTAL, cellulose HPM 603 (binder) and AVICEL PH 102 (binder, filler, disintegration-promoting excipient) in a mixer, preferably in a high-speed mixer (DIOSNA, LOEDIGE, FIELDER, GLATT etc.). Add water as granulation liquid to the mixture, and knead in a mixer, preferably a high-speed mixer, until an adequate consistency is achieved. Alternatively, the binder cellulose HPM may be dissolved in the granulation liquid, water, beforehand. Granulate the wet granules using a suitable device (ALEXANDER Reibschnitzler, QUADRO-COMILL) and dry in a fluidised bed (AEROMATIC, GLATT). Add AVICEL PH 102, AEROSIL 200 (flow conditioner) and polyvinylpyrrolidone PXL (disintegrator) to the dry granules and comminute and mix in a comminuter (FREWITT, QUADRO-COMILL, FITZMILL). Finally, add magnesium stearate (lubricant) and mix (STOECKLIN container mixer, VRIECO mixer). Alternatively, the lubricant may be added directly to the comminuted material. Compress the final mixture to form TRILEPTAL tablets (eccentric press, rotary press: KILIAN, KORSCH, FETTE, MANESTY).

Coat the tablets with an aqueous preparation consisting of cellulose HPM 603 (film former), iron oxide yellow 17268 (pigment), PEG 8000 (plasticiser for the film former), talcum (anti-adhesive agent, covering agent) and titanium dioxide (covering agent) in a rotating coating pan (ACCELA-COTA, GLATT, DRIACOATER, DUMOULIN). Alternatively, it is possible to use, for example, fluidised-bed or air-suspension apparatus for the coating process (AEROMATIC, GLATT, FREUND, HUETTLIN).

Example 2

	(mg)	(mg)	(mg)
Tablet Core:			
Oxcarbazepine	150,0	300,0	600,0
AviceIPH 102	28,8	57,5	115,0

Cellulose HPM 603	5,0	10,0	20,0
Nymcel ZSB 10	13,8	27,5	55,0
Aerosil 200	1,3	2,5	5,0
Magnesium Stearate	2,3	4,5	9,0
Total:	**201,0**	**402,0**	**804,0**
Coating:			
Polyethylene glycol (PEG) 8000	0,915	1,497	2,328
Cellulose HPM 603	5,054	8,269	12,865
Talcum	3,659	5,988	9,314
Titanium dioxide	1,029	1,684	2,62
Iron oxide, yellow	0,343	0,561	0,873
	11	**18**	**28**
Total	**212,0**	**420,0**	**832,0**

The oxacarbazepine, cellulose HPM 603 and Avicel PH 102 are mixed together in a planetary mixer (Aeschbach). Alcohol is added to this mixture before it is kneaded in a planetary mixer until a desired consistency is achieved. Thereafter the methodology according to Example 1 is followed to provide coated tablets.

Example 3

	(mg)	(mg)	(mg)
Tablet Core:			
Oxcarbazepine	150	300	600
Avicel PH 102	46	92	184
Cellulose HPM 603	6	12	24
Polyvinylpyrrolidone	10	20	40

Aerosil 200	0,8	1,6	3,2
Magnesium stearate	2,2	4,4	8,8
Total:	**215**	**430**	**860**
Coating:			
Polyethylene glycol (PEG) 8000	0,915	1,497	2,328
Cellulose HPM 603	5,054	8,269	12,865
Talcum	3,659	5,988	9,314
Titanium Dioxide	1,029	1,684	2,62
Iron oxide, yellow	0,343	0,561	0,873
	11	**18**	**28**
Total	**226**	**448**	**888**

The same methodology as Example 1 is carried out on the formulation to provide coated tablets.

Claims

1. A formulation comprising oxacarbazepine having a median particle size of approximately 2 to 12µm, preferably 4 to 12 µm, more preferably 4 to 10 µm and with a maximum residue on a 40 µm sieve of up to 5%, e.g. 2%.

2. A film-coated tablet comprising oxacarbazepine having a median particle size of approximately 2 to 12µm, preferably 4 to 12 µm, more preferably 4 to 10 µm and with a maximum residue on a 40 µm sieve of up to 5%, e.g. 2%.

3. A film-coated tablet which comprises,
a) a tablet core comprising a therapeutically effective dose of oxacarbazepine, preferably being in a finely ground form, having a median particle size of approximately from 4 to 12 µm, preferably 4 to 10 µm with a maximum residue on a 40 µm sieve of up to 5%, e.g. 2 %, and further excipients that are suitable for the production of granules; and
b) a hydrophilic permeable outer coating.

4 A film-coated tablet according to claim 3, which comprises
a) a tablet core comprising a therapeutically effective dose of oxacarbazepine, preferably being in a finely ground form, having a median particle size of approximately from 6 to 8 µm with a maximum residue on a 40 µm sieve of 2 %, and further excipients that are suitable for the production of dry granules.

5 A film-coated tablet according to either claim 3 or claim 4, which comprises as component b) a hydrophilic permeable outer coating comprising white pigments, iron oxide pigment and optionally further excipients.

6. A process for the production of a film-coated tablet containing oxacarbazepine comprising forming the oxacarbazepine, having a median particle size of approximately from 2 to 12µm, preferably 4 to 12 µm, more preferably 4 to 10 µm with a maximum residue on a 40 µm sieve of up to 5%, e.g. 2 %, and optionally other excipients into a central core, and coating said core with a hydrophilic permeable outer coating.

7. A process for producing a film-coated tablet according to claim 3, which comprises finely grinding the oxacarbazepine to a median particle size of approximately from 2 to 12µm, preferably 4 to 12 µm, more preferably 4 to 10 µm with a maximum residue on a 40 µm sieve of up to 5%, e.g. 2 %, and, with the admixture of excipients that are suitable for granulation processes, forming the active ingredient into granules, compressing the granules to form tablet cores using conventional tabletting processes, and providing the cores with a hydrophilic permeable outer coating.

8 A process according to claim 7, which comprises forming the finely ground oxacarbazepine into wet granules with the admixture of excipients that are suitable for granulation processes, and compressing the wet granules to form tablet cores using conventional tabletting processes.

9. Oxacarbazepine having a median particle size of approximately 2 to 12µm, preferably 4 to 12 µm, more preferably 4 to 10 µm.

10. Oxacarbazepine having a median particle size of approximately 2 to 12µm, preferably 4 to 12 µm, more preferably 4 to 10 µm and with a maximum residue on a 40 µm sieve of up to 5%, e.g. 2%.

US Case **4-21233A**

DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

☒ Original ☐ Supplemental ☐ Substitute

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

OXACARBAZEPINE FILM-COATED TABLETS

the specification of which:

☐ is attached hereto.

☐ was filed on _____ (day/month/year) as Application No. _____

and, if this box (☐) contains an *

☐ was amended on _____ (day/month/year)

☒ was filed as Patent Cooperation Treaty international Application No.

PCT/EP 98/00794 on **12/02/98** (day/month/year)

and, if this box (☐) contains an *

☐ entered the national stage in the United States and was accorded Application No.

_____

and, if this box (☐) contains an *

☐ was amended, subsequent to entry into the national stage, on _____ (day/month/year)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above and, if this application was filed as a Patent Cooperation Treaty international application, by any amendments made during the international stage (including any made under Patent Cooperation Treaty Rule 91, Article 19 and Article 34).

I acknowledge my duty to disclose all information which is known by me to be material to the patentability of this application as defined in 37 C.F.R. § 1.56.

I hereby claim the benefit under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below and under 35 U.S.C. §365(a) of any Patent Cooperation Treaty international application(s) designating at least one country other than the United States listed below and have also listed below any foreign application(s) for patent or inventor's certificate and Patent Cooperation Treaty international application(s) designating at least one country other than the United States for the same subject matter and having a filing date before that of the application the priority of which is claimed for that subject matter:

COUNTRY/REGION (OR P.C.T.)	APPLICATION No.	FILING DATE (day/month/year)	PRIORITY CLAIMED
Switzerland	**331/97**	**14/02/97**	☒ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

I hereby claim the benefit under 35 U.S.C. § 119 (e) of any United States provisional application(s) listed below:

APPLICATION NO.	FILING DATE (day/month/year)

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) listed below and under 35 U.S.C. §365(c) of any Patent Cooperation Treaty international application(s) designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in said prior application(s) in the manner required by the first paragraph of 35 U.S.C. §112, I acknowledge my duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date(s) of the prior application(s) and the national or Patent Cooperation Treaty international filing date of this application:

United States Application No.	United States Filing Date (day/month/year)	Status (Pending, Abandoned or U.S. Patent No.)	International Application No. and Filing Date

I hereby appoint the registered practitioners associated with Customer No. 001095, respectively and individually, as my attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Full name of sole or first joint inventor	**Burkhard SCHLÜTERMANN**
Inventor's signature	Burkhard Schlütermann Date 30/06/93 (day/month/year)
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IMPORTANT: Before this declaration is signed, the patent application (the specification, the claims and this declaration) must be read and understood by each person signing it, and no changes may be made in the application after this declaration has been signed.